NON-SPECIFIC PROTEIN THERAPY

Thesis submitted for the

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by

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SECTION I.

Introduction

The favourable reaction often observed when an acute infection occurs in the course of a chronic condition is well-known, e.g. when pneumonia results in the improvement of a case of psoriasis, where previously all recognised treatments had failed, or when an attack of erysipelas causes an amelioration of a long-standing case of lupus vulgaris. From these clinical facts there has gradually emerged a form of therapy, which has as its main object the production of an acute reaction to oust a chronic process. There will be a criticism that it is an empirical treatment based on no sound scientific principles; this is true to a certain extent in that no satisfactory explanation has yet been put forward as to how these favourable reactions are produced. Nevertheless, that it is an important form of treatment is shown by the fact that the topic has attracted a good deal of attention among both clinicians and laboratory workers and the large volume of published work demands at least attention.

Like any other new treatment, it has been much abused, and hailed as a cure for all diseases. This is not so, and is only of value when used with care

and judgment, and in certain diseases.

Those ills which are believed to be due to sensitisation of the body to a foreign protein react well to this form of therapy. In this category are included such diseases as asthma, hay fever, urticaria and angio-neurotic oedema. By means of skin tests, a specific protein may be found as a causal agent in these conditions, and desensitisation of the patient can be carried out by giving gradually increasing injections of the specific protein; similar or better results can be attained by the injection of non-specific protein, and by such dissimilar proteins as peptone and tuberculin, which have been used with equal success in the treatment of asthma. Urticaria is not the only skin disease to react favourably, for others, which have no known relation to protein sensitisation, also respond well, e.g. cases of general pruritus, furunculosis, psoriasis, dermatitis herpetiformis, pregnancy dermatitis, ringworm, lupus erythematosus, lupus vulgaris, pemphigus and chronic eczema.

In syphilis, too, non-specific protein has its place. Although it has been treated in all stages of the disease, it has its greatest value in the late case of syphilis, e.g. cases of gummata and nerve syphilis. The most striking results are to be found

in cases of general paralysis of the insane. In this condition, many substances, known to produce a reaction in the patient, have been tried; included in these are milk, sodium nucleinate and typhoid-paratyphoid vaccine, and more recently, malarial therapy, to produce a similar effect, has been introduced. In gonorrhoea, the most favourable results are obtained in the complications of the disease, such as arthritis, epididymitis, vesiculitis and prostatitis.

Some cases of mental and nerve disease respond favourably. That irregular illness, dementia praecox, is favourably influenced. Cases of toxic confusional insanity also react well. Deschamps[1] records a case of furunculosis and mania in the same patient, which both disappeared together and rapidly by the action of non-specific protein. In encephalitis lethargica, the effects of the treatment are only transient and in epilepsy there have been varying results.

Into eye disease, also, non-specific protein has recently made its way and it has been used with success in cases of gonococcal conjunctivitis, iritis, and sympathetic ophthalmia.

The previously recorded relation between acute and chronic processes, suggested to Coley, the production of an acute infection, as a therapeutic

measure. He accordingly introduced Coley's fluid in the treatment of malignant disease, particularly sarcomata. Although the original claims for this treatment have not been substantiated, it is a valuable form of therapy in sarcomata, treated by a combination of excision and protein.

Of acute infections, erysipelas, which it was previously noted, sometimes resulted in the amelioration of a chronic process, is itself favourably influenced by protein. Anthrax too, sometimes responds well.

The subject of these notes has been suggested to me by personal observation, on several occasions, that chronic disease is frequently benefited by the occurrence of an acute condition. I have also had the desire to personally experience the reactions and results from non-specific protein. It seemed to me fairly easy to understand how the body defence could be stirred up in chronic disease, where there always appears to be a kind of impasse between patient and treatment; the treatment appeared to me less rational in acute disease, where presumably the defence mechanism is fully employed. I have accordingly tried the effect of such varied methods as milk, typhoid-paratyphoid vaccine, tuberculin and malarial therapy in cases of erysipelas, arthritis,

asthma and general paralysis of the insane respectively. These cases have been treated and observed at the Stepping Hill Hospital, Stockport, during the period 1930-1932. My purpose is to show that this treatment is valuable if used with care and not in a haphazard fashion. I do not wish to belittle the value of other treatments in these diseases, nor do I advise the treatment as a routine. Many cases of asthma, arthritis and general paralysis of the insane, respond well to drug or other remedial measures, but many cases do not, and it is in this latter type of case that non-specific protein would appear to be indicated. Erysipelas is a disease which is self-limited in the majority of cases; sometimes, indeed, it shows no signs of limiting itself but spreads from one part of the body to the other; sometimes it recurs in the same patient and in the same place two, three or more times. It is in these latter two types, I hope to show, that injections of milk have a therapeutic value.

SECTION II

Historical

The treatment of disease by sera and antitoxins was first put on a rational basis by the discovery in 1893 of diphtheria antitoxin by Emil von Behring, for the treatment of diphtheria. The demonstration of 'Phagocytes' by Metchnikoff in 1884 led to the period of specificity in treatment, led by Sir Almroth Wright. He originated general vaccinotheraphy in 1902, and in 1906 Wright and Douglas discovered a substance in normal serum, which in conjunction with leucocytes was capable of phagocyting bacteria. To this substance the name Opsonin was given and it was decided that the estimation of Opsonin in the infected individual might afford an index of the degree of immunity in staphylococcal infections. One point on which great stress was laid was the occurrence of a negative phase after the injection of a vaccine, and it was noted that after a dose of vaccine there was a primary fall in the opsonic index followed by a rise. From these observations there followed a system of immunisation, which was regarded as being safe only when the system of dosage was controlled by periodical estimations of the opsonic index.

During this period of treatment of disease by

specific vaccines, observations were made by different observers which appeared to throw doubt on this specificity. Rumpf[2] in 1893 showed that a series of typhoid patients treated with B. Pyocyaneus vaccine reacted favourably. In 1891, Horbaczenski[3] introduced nucleins in the treatment of lupus vulgaris and showed that a focal reaction could be elicited just as well as by tuberculin, which had been introduced by Koch in 1890. In 1895, Matthes[4] demonstrated that the tuberculin reaction could be equally well produced if dextro-albumose were used. About the same time, Fochier[5] introduced the 'fixation abscess' method of treating pyogenic infection. In 1894, a similar treatment was introduced by Gilbert[6], who injected pleural fluid into a patient suffering from pleurisy with effusion.

From 1906 onwards vaccines were given an extended trial particularly in typhoid fever. It is true that increased antibody production could be proved by estimation of the opsonic index but the patient was not cured. In 1912 Ichikawa showed that when he treated cases of paratyphoid fever with typhoid vaccine, good results were seen in several cases; he concluded therefore that the result could not be due to a specific reaction. Kraus and Ludke showed that similar results could be obtained by

injection of B.Coli vaccine. From these observations it became evident that as good clinical results could be obtained by non-specific as by specific therapy. The next stage in the development of this non-specific therapeutic measure was the injection of bacterial components and bacterial split products, followed by protein split products of non-bacterial origin and finally, any substance which produced a reaction in the patient and which was followed by a similar result beneficial to the patient.

While these results were being demonstrated, the chemistry of proteins was being investigated by several chemists. In 1896, Albrecht Kossel discovered histidin and gave a classification of proteins. Emil Fischer during the period 1896-1906 succeeded in linking together as many as eighteen molecules of amino-acids in vitro and obtained compounds giving the reactions of proteoses. Much of the credit of the chemistry of bacteria is due to Vaughan and his co-workers,[7] who have identified many of the usual amino-acids of proteins among the products of hydrolysis of bacteria.

The first experiment on anaphylaxis or supersensitisation of the tissues was performed by Francois Magendie[8] in 1839, who proved that secondary or subsequent injections of egg-albumin cause death in

rabbits tolerant to an initial injection. In 1909, the term 'anaphylaxis' was introduced by Charles Richet, although the same condition had been demonstrated previously by Theobald Smith, from the bacterial products of diphtheria, and called by Ehrlich the "Theobald Smith Phenomenon".

One of the first clinical records of this non-specific therapy was made by Beard[9] in 1911, who introduced the so-called enzyme treatment of cancer, which consisted in injecting subcutaneously a trypsin solution. No case of malignant disease was ever actually cured, but a focal reaction resulting in a diminution of the size of the tumour and a general reaction were frequently observed. In 1913 Coley's fluid was introduced; this contained the combined toxins of streptococcus erysipelas and b. prodigiosus and was an attempt to favourably influence the course of inoperable sarcoma by producing a severe local and general reaction. It was used successfully in a case of mixed-cell sarcoma, treated first by excision and then by injection of small doses of Coley's fluid[10]. Since that date this treatment has been given an extended trial with varying results although McNamara[11] records three cases saved by it. In 1916 Saxl[12] introduced intragluteal injections in the treatment of various diseases, and since 1921 almost

every known disease has been treated by non-specific protein methods.

In 1916 also Miller and Lusk[13] published the first series of cases of arthritis treated by non-specific means. They used typhoid vaccine and preparations of proteose in acute rheumatism, sub-acute rheumatism and chronic gonorrhoeal arthritis. Auld[14] found little or no benefit resulted unless he used 'veal peptone' although he considers that typhoid vaccine is the more effective protein to use. Cecil records the effect in 40 cases of acute arthritis; he used T.A.B. vaccine and found that 40% of cases of acute rheumatic fever recovered without the use of salicylates. Snyder and Ramirez[15] treated 70 cases of chronic arthritis with 8.5% cures, using T.A.B. vaccine and secondary proteoses from milk. Betz[16] reports on 50 cases; the acute cases cleared up as a rule, after the first injection. Middleton[17] used b.coli or typhoid vaccine in 10 cases; the disease in the acute cases was arrested and relieved in the chronic ones. Perkins and White[18] used T.A.B. vaccine successfully in 6 cases of rheumatoid arthritis. Stockman and Campbell[19] have used typhoid vaccine in 70 cases and Paul[20] administered vaccine by scarification in 700 cases, 65% of which were cured and 95% benefited. Nolf[21] is of the opinion

that injections of peptone make salicylate treatment more efficacious in certain obstinate cases of rheumatic polyarthritis. Yeoman[22], using T.A.B. vaccine intravenously, holds the view that sciatica of the sacro-iliac joint can be best treated by this method.

Although vaccines have been extensively used in arthritis non-specific peptone has also been used. Bulmer[23] records the success of three or four intramuscular injections of peptone in cases of fibrositis. According to Eason[24] rheumatoid arthritis showed improvement after peptone. Goodall[25] has used it in cases of arthritis deformans.

The treatment of bronchial asthma by immunisation with small graded doses of peptone has been employed with success. To A. G. Auld[26] is due the credit of introducing this mode of therapy in 1917 and since this date he has made numerous contributions to the literature on the subject. H. Warren Crowe[27] uses peptone as an aid to vaccine treatment.
I. C. Walker[28] was the pioneer in introducing cutaneous tests to discover the offending protein in asthma, but according to Langdon Brown[29], asthmatics show sensitiveness only occasionally to a particular protein, hence the skin test is only reliable in a small percentage of cases.

In 1921, Professor Van Leeuwen[30], as a result of his observation that a considerable number of asthmatic patients were sensitive to tuberculin as shown by the cutaneous tests, introduced the treatment by old tuberculin. This is not a specific treatment and it acts merely by virtue of its protein content.[31] Nelson[32] has used the treatment successfully in three cases. T. M. Ling[33] has reported good results following upon the use of this method in a series of 24 children. Simpson and Stone[34] have reported 9 cases. In 1930, Maxwell[35] gave a preliminary report on a series of 36 cases, treated by this method and in 1932 he made a further report[36], coming to the conclusion that there is a tendency to relapse, so that the results are not so favourable as those previously recorded.

There has been much written on the subject in regard to mental and nervous disorder. Videla[37] used 5% witte peptone in 218 cases of insanity and 140 of these cases were discharged as 'recovered'. Robb[38] injected the patients own serum in cases of toxic confusional insanity with a fair measure of success. In cases of dementia praecox the results have been encouraging. Templeton[39] considers the improvement following malarial therapy to be of a fleeting character. Under sodium nucleinate many

cases are said to have recovered completely and others to have shown decided improvement[40]. Lundvall[41] records four recoveries in 18 cases. Lepine[42] in 13 cases of dementia praecox had no success but in 13 cases of manic depressive insanity obtained eight cures and two improvements. Sir J. Purves Stewart[43] treated 29 cases of disseminated sclerosis by weekly injections of T.A.B. vaccine and eight of these greatly benefited, and maintained the improvement for two years.

In 1887, after suggesting (but without trying) the use of malaria for treating general paralysis of the insane, and after failures by apparently analogous means, Dr. Wagner-Jauregg[44] introduced in 1917-1919 his treatment by 'induced malaria'. This idea of pyrexial treatment had been elaborated and prosecuted in Scotland some forty years ago by Dr. Lewis C. Bruce[45]. Sir J. Purves Stewart[46] quotes a dissertation by Koster written in 1848 on the beneficial effects of malaria on insanity. The same idea lies behind the introduction of very hot baths in the treatment of cases of tabes dorsalis by Mehitens and Pouppirt[47] in 1929. The first case of general paralysis treated by malaria in this country was of a male patient at Whittingham Mental Hospital[48] who was inoculated on 21st July, 1922. McAlister[49]

records 12 cases treated by this method. Bunker[50] compares this mode of therapy with injections of trypaisamide; 27% of the cases treated by the former method remitted while 35% of cases remitted after the latter treatment. Meagher[51] gives the mortality in the first two months of malarial therapy as 40%. R. Lees[52] records 50 cases treated by this method. Silverston[53] records a case with inconclusive result, treated with African tick fever.

In gonorrhoea, milk has been frequently employed. M. W. Browdy[54] considers this a successful and safe therapeutic measure in acute or subacute gonorrhoea. D. Lees[55] uses this non-specific protein in complicated cases of gonorrhoea, e.g. vesiculitis, prostatitis, epididymitis, arthritis. Smith[56] reports the injection of horse serum in cases of gonococcal arthritis with satisfactory results.

Non-specific protein in the treatment of skin disease originated from specific protein therapy. Specific desensitisation can be carried out when it is possible to identify the causal antigen - as in the case of urticaria brought about by some article of diet - by the device of administering a minute portion of the food substance one hour before the meal is taken, a method first employed by Pasteur, Vallery-Radot and Lucien Rouques. Where the nature

of the exciting agent cannot be ascertained exactly, one of the non-specific methods may be substituted, often with equally satisfactory results. Chronic cases of urticaria, seborrhoea, seborrhoeic eczema, dermatitis due to irritants and chronic skin conditions generally are affections in which good results are obtained from a 5% solution of peptone intravenously[57].

Into ophthalmic practice protein shock therapy has been lately finding its way. In 1911, Röhmer used autohaemotherapy against gonorrhoeal conjunctivitis, employing the principle demonstrated by Eckart in 1894 that injected or transfused blood acted as a chemical stimulant. Dr. Shorney[58] advocates the injection of cows' milk and quotes German and Russian work on the subject; he uses it in gonococcal ophthalmia inflammation of the uveal tract, and he believes that it will abolish the risk of sympathetic ophthalmia after perforating wounds of the eye.

Acute infections such as erysipelas and anthrax also benefit by non-specific protein. A. C. McEachern[59] records the successful use of milk in the former Vaccarezza[60] and his co-workers find that the daily intramuscular injection of a 3% solution of peptone in cases of anthrax gives as good results as

specific serum.

It is doubtful whether X-ray treatment should be included here, because M. Giraud, G. Giraud and Pares[61] record a case of myeloid leukaemia in which the tolerance to X-rays was good until after a period of five years when it diminished so that after each exposure to X-rays there followed a transient crisis described as anaphylactic in nature. The responsible cause was regarded as sensitisation of the body by proteins liberated by the destruction of the leucocytes by X-rays.

SECTION III

The physical properties of proteins are those of colloid substances, i.e. they do not form crystals nor do they pass through an animal membrane. There are exceptions, e.g. peptone which is capable of passing through an animal membrane. Chemically, the proteins are relatively stable, inert and capable of acting either as an acid or a base. They can be hydrolysed by the action of superheated steam or by boiling with acid or alkali; the protein takes up water and itself becomes split up into smaller molecules. The molecule becomes progressively smaller and is converted into a metaprotein. The next stage in disintegration is the formation of a series of hydrated proteins, firstly proteoses and later peptones. If the hydrolysis be continued polypeptides, which do not show protein characteristics and which consist of groupings of amino-acids are formed. The last degradation products are the amino-acids.

Chemistry of Proteins:

These products resulting from the breaking down of protein molecules are commonly referred to as protein split products and they vary in character, in

amount and in composition with the protein undergoing lysis and the method used in bringing about the disintegration.

Proteins are composed of the chemical elements carbon, hydrogen, oxygen, nitrogen, sulphur and sometimes phosphorus. They are classified as:

(a) Simple or naturally occurring proteins, e.g.:

1. Protamines, chiefly found in combination with nucleic acid, e.g. in spermatozoa of certain fishes.

2. Albumins and Globulins, which occur in all cells and in many fluids of the body.

3. Histons, e.g. globin found in haemoglobin.

4. Phosphoproteins, e.g. caseinogen found in milk. These contain phosphorus in addition to the five elements common to proteins generally.

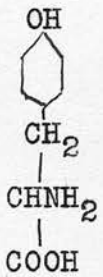
5. Sclero-proteins form the chief constituents of fibrous tissue.

(b) Compound proteins, i.e. a combination of protein with some other substance. Nucleo-protein is a constituent of all cell nuclei and consists of protein combined with nucleic acid. A gluco-protein is the combination of a carbohydrate radical with protein. Chromoproteins are those in which the non-protein part of the molecule is coloured, e.g. haematin in haemoglobin.

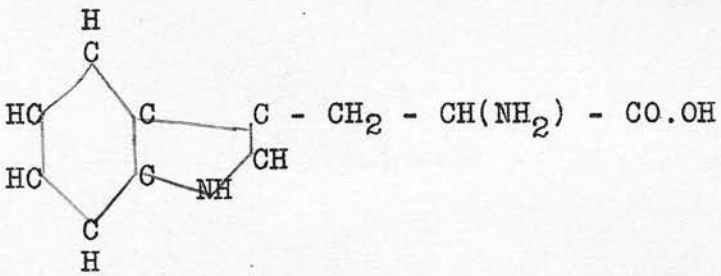
The amino-acids, which form the end-product of disintegration of every protein molecule are derived

from the fatty acids by the replacement of a hydrogen atom of the NH_2 group, e.g. the formula of acetic acid is CH_3COOH and that of amino-acetic acid is CH_2NH_2COOH. More complex compounds are formed from more complicated acids.

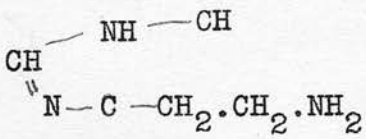
Tyrosine is oxy-phenyl-amino-propionic acid represented by the formula



Tyrosine is indol-amino-propionic acid represented by the heterocyclic, indol grouping



Histamine is beta-iminazol-ethylamine represented thus



and is derived from histidine by the loss of a single CO_2 molecule.

All the amino-acids have both acid and basic properties. The many amino-acids which enter into the structure of the protein molecules are capable of

almost innumerable groupings and each fresh grouping will produce a distinct protein; they are however all alike in their breaking down, in that they all yield the same simple end-products, such as urea and carbon dioxide.

Metabolism of Proteins:

The proteins are completely broken down into their constituent amino-acids by the erepsin in the succus entericus. The acids are absorbed as such into the blood stream and can be demonstrated there. There is no evidence that they can be resynthesised into protein during their passage through the intestinal villi as in the case of fats. The amino-acids are taken up by the liver, the muscles and other tissues to be used either for the repair of tissues or in the production of energy. In the liver, the acids are deaminised, i.e. the amino-group (NH_2) is replaced either by O_2 or by an OH radicle, ammonia is set free and this is converted into urea.

Some observers report the finding of albumose in normal blood but if present the amounts are extremely minute, and the evidence that these traces of nitrogenous material are truly proteoses is not conclusive. In conditions in which ulceration or other lesion is present in the intestine, it is possible to find small amounts of proteoses in the urine, but

not in quantities sufficient to account for any appreciable intoxication, although proteoses are toxic. Widal[62] and his fellow-workers, experimenting on dogs, observed changes in the blood following the ingestion of protein; these changes he described under the name of the 'haemoclasic crisis' and consisted in increased coagulability and a leucopenia. He found similar changes in the blood of human beings after the ingestion of milk, especially if the liver function were damaged. This experimental and clinical evidence led Widal to postulate a proteopexic function of the liver, whereby in normal circumstances, toxic products of digestion were prevented from entering the general circulation.

Each successive step in the building up and breaking down of proteins and individual fractions of proteins is the work of a special enzyme, e.g. there is evidence to show that the fractions of proteins such as tyrosin and tryptophane are dealt with each in a special manner and in successive stages.[63] It is not always possible to demonstrate the products of these successive stages because they merge imperceptibly one into the other. If this natural process fails, the intermediate product will escape further change and may be demonstrated, e.g. in alkaptonuria,

a condition in which the urine darkens when it comes in contact with the air. In this condition, homogentisic acid is present in the urine, due to a congenital lack of an enzyme, which has the function of splitting the benzene ring of the aromatic protein fractions, tyrosin and phenyl-alanin. In 1930, Best and McHenry[64] discovered a special ferment, histaminase, which has the function of destroying histamine, which is not a normal protein fraction of the body. Cystinuria is another example of an arrest of metabolism; in this condition there is a lack of disseminating enzymes which as Long[65] has shown are widely distributed in the tissues. This deficiency results in the excretion of unchanged cystin, which normally is broken down into its constituent amino-acids.

Antigenic Properties of Proteins.

All soluble proteins with one exception, which is the complicated protein of Dakin, are capable of acting as antigens, i.e. they cause the generation and appearance in the blood of specific antibodies, when introduced into the blood or tissues of the body. They act as such, because they are colloids. It appears that an antigen must be a colloidal molecule, and only if the molecule is of such a size that it cannot diffuse into the cells and be destroyed; if

it cannot enter the cell it incites the cells to form destructive extracellular antibodies as a protective measure. Of the cleavage products of proteins, the amino-acids and polypeptides do not act as antigens and the proteoses are antigenic to only a slight degree if at all[66]. Whether the entire protein molecule or only groups thereof determine the characteristic of an antigen is not known; there is evidence to support either view. Wells and Osborne[67] have shown that a single protein can produce more than one antibody.

Foreign Proteins:

In many instances the injection of a foreign protein into an animal produces severe and sometimes fatal intoxication. Almost any non-toxic soluble protein may be made toxic for animals by giving the animal a small dose of the protein eight days previously. This preliminary dose, renders the animal hypersensitive to the same protein, so that a relatively small amount of an otherwise entirely harmless protein produces violent, often fatal, symptoms when introduced into the blood. This is known as anaphylaxis and its manifestations vary in different animals, e.g. a guinea pig shows signs of asphyxiation through spasm of the bronchioles with permanent

emphysematous distension of the alveoli of the lungs. In dogs the chief effects are on the blood pressure, which is very much reduced and is accompanied by marked engorgement of the liver. The injection of blood from a sensitised animal into the blood of another animal after a latent period of fifteen to eighteen hours, produces similar, although not so severe, reactions. This condition is not, however, confined to animals for a second injection of serum or antitoxin in an individual ten days after the first causes severe shock immediately or soon after the injection; this shock is characterised by sudden prostration and exhaustion of the whole circulatory system, especially the heart, with cyanosis, extreme dyspnoea and very feeble pulse.

Possibly, anaphylaxis is the result of an exaggeration of the normal process of defence of the body against foreign proteins by means of digestion. Normally this is accomplished in the alimentary tract by the erepsin of the intestinal juice, if the protein escapes this process, it is acted upon by the enzymes of the blood and tissues. Injection of a protein is such an unnatural process that the body is stimulated to produce proteolytic substances in excess. When the second dose is injected, these ferments break off histamine from the injected

protein, and this produces its usual toxic effect. There is not universal agreement however that histamine causes the intoxication. Vaughan has shown that proteins boiled with an alcoholic NAOH solution might be split into two fractions, one toxic and alcohol-soluble, the other non-toxic and insoluble in alcohol. The toxic fraction of the protein, called protein poison produces symptoms in animals identical with anaphylaxis. Anaphylaxis has been defined as the last stand of the race against adulteration of its protoplasm, and proteins excite it in varying degrees. If the protein injected is going to produce an enormous change in the bodily structure, then the anaphylaxis is fatal; if the changes are not going to be so severe, anaphylaxis declares itself in violent attempts to get rid of the protein.

In certain diseases such as asthma, hay fever and angio-neurotic oedema, there is an inborn resentment to certain proteins, and the manifestations of these diseases are the efforts of the body to get rid of the offending protein. Such protein may be introduced in food (e.g. eggs) in animal or vegetable dust (pollen, the dandruff of a horse or cat) or by organisms. These diseases are sometimes known as the allergic diseases, because they are due to a protein sensitisation or allergy. Desensitisation can be

produced by injecting small doses of the offending protein, i.e. specific protein or by small doses of non-specific protein, e.g. peptone. It is in this state of allergy that non-specific protein therapy gives its best results.

The Non-specific Reaction.

Anaphylaxis and allergy simulate to a considerable degree the picture that is obtained in non-specific therapy. The reaction will vary with the substance used, its mode of application and its dosage; the condition of the patient and the number of previous injections. An intravenous injection gives a more rapid and more severe reaction than an intramuscular one; a bacterial antigen usually produces a greater general disturbance of the patient than a non-bacterial one, e.g. the protein split products. The reaction varies from a leucocytosis, to mild febrile reactions, and to extreme pictures of shock and prostration. The reaction produced after intravenous injection of typhoid vaccine may be taken as the type. The patient complains of a chill or rigor, usually occurring within thirty minutes of injection. He becomes cold and asks for more bedclothes; he next becomes warm and finally he passes into a stage in which he is bathed in perspiration.

The temperature rises to 100° or 101° F; if the temperature rises from normal, above these, then the reaction is excessive and probably due to an overdose of vaccine. The pulse varies with the temperature and is usually increased by fifteen to twenty beats per minute. The patient feels uncomfortable and complains of headache and sometimes nausea and vomiting. Other observations such as increase in blood pressure, the appearance of herpes or urticaria, and an increase in nitrogen metabolism may be noticed. Blood changes such as leucocytosis, the occasional appearance of nucleated red cells in the blood, an increase in platelets, blood sugar, fibrinogen and thrombokinase, do occur. There are also focal reactions, e.g. in arthritis the joint becomes more painful and swollen and there is an increased limitation of movement. All these are followed by a stage of euphoria, in which the local and general condition shows improvement.

Specific protein differs from non-specific in that the therapeutic results observed are not the outcome of a reaction on the part of the patient, but the direct effect of that protein on the causal agent of the disease. To take examples of this, diphtheria antitoxin neutralises the toxin produced by the bacillus diphtheriae as also does the tetanus

antitoxin neutralise the poison produced by the tetanus bacillus. Antitoxic serum contains approximately 7-8% of protein and is usually obtained from a horse; thus, when injected into the human being, it would act as a foreign protein. A large dose of antitoxic or antibacterial serum might be fatal on first injection by producing anaphylaxis; usually, however this does not happen unless the patient has had an injection of serum some time previously unknown to the medical attendant, or the latter has given a second injection eight days after the first. A mild form of protein reaction is very often observed eight to nine days after the first injection, characterised by widespread urticarial rash, fever and prostration, besides joint and muscle pains, oedema and adenitis. This is called serum-sickness and usually passes off in a few days.

The Mechanism of Protein Reactions.

That beneficial results follow the injection of foreign protein in certain diseases is undenied; there is not universal agreement, however, as to which manifestation of the reaction produced is responsible for the therapeutic result. The chill, the fever, the sweat and the leucocytosis might all be assumed to have some bearing on the beneficial result. It is known that an intercurrent disease

showing all these signs, very often favourably influences the course of a chronic disease, occurring in the same individual. Some of the non-specific protein methods, e.g. the injection of T.A.B. vaccine, aim at inducing fever, or artificial malaria in the treatment of general paralysis; however, others, such as whole blood injections, do not invoke or require a febrile response. It would thus seem that some other reason must be sought for the striking clinical effect that sometimes follows non-specific injections.

Leucocytosis follows a primary leucopenia; the clinical effect produced appears to bear no relation to the extent of the leucocytosis for favourable results may be produced in cases that show little or no increase in the white cell count. In malarial therapy there is a leucopenia throughout and therefore beneficial results in general paralysis insane cannot be explained on this theory. Many observers lay stress on the increase in proteolytic ferments, which are of importance in overcoming any infection. A possible explanation is that the foreign protein stimulates the tissues that form antibodies, so that they produce not only antibodies for this antigen but also for the antigens of the specific aetiological factor of the disease. Larson's[68] theory is

that many bacteria such as streptococci and pneumococci are imperfect antigens; these produce antibodies which are specific but they do not possess the second essential, viz. the stimulus that is necessary to cause the antibodies to be cast off into the blood stream. He arrives at the conclusion that the injection of foreign protein enables the organism to throw off the so-called sessile bodies into the circulation. Hermann[69] concludes that the injection of foreign protein serves as a stimulus for the liberation of specific antibodies in animals in which previously injected antigen was unable to do so. This theory was recently investigated by Ling[70] who injected various foreign proteins into normal human beings. He found that serum antibodies including bacteriolysins for b. typhosus and staphylococcus aureus were shed into the circulation within twenty four hours of injection. He found that the most effective agents to produce this as well as the leucocytosis were the bacterial protein, typhoid vaccine and market milk - the latter being better than certified milk which contains less organisms. It has also been found that antibodies which have disappeared after infection or following immunisation artificially produced again returned to the serum after any procedure that increased the body tempera-

ture by influencing the thermal centre of the brain or by injecting pyrogenic drugs. This tends to show that increased temperature has a direct stimulating effect on the previously formed antibodies.

Since the effect of non-specific protein on the temperature varies, it is unlikely that Paltauf's[71] suggestion that vaccine causes a paralysis of the heat-regulating centre in the medulla is the correct one. Also, as the fall in temperature following injection is often a permanent one, there must be, on this theory, a permanent paralysis of the centre. There is no proof that this ever occurs.

A focal reaction is a matter of common observation in non-specific therapy, e.g. in a joint there is an increase in pain and tenderness, followed by a period of comparative comfort. These observations may be explained (1) by the increase in the permeability of the capillaries of the part resulting in swelling and pain, (2) by increased digestion at the focus of inflammation resulting in an absorption of protein products and therefore causing an aggravation of the systemic condition.

The Chemical Factor in Non-specific Therapy.

Since injections of proteins, protein split products, and measures, which appear to act by de-

stroying the body cells, produce a similar reaction, it is probable that the active principle is a product of protein decomposition. As a general rule, it has been observed that the first products of protein hydrolysis are the most toxic and with further cleavage the toxicity lessens and finally disappears, e.g. Wolf[72] has shown that the amino-acids and polypeptides do not cause a fall in blood pressure. Proteoses, on the other hand, are distinctly toxic. Besides, the classical effect of inhibiting the coagulation of the blood, the proteoses have a lymphagogue effect and cause a marked febrile reaction. They have little power in stimulating antibody formation. Whipple[73] in studying the problem of intestinal obstruction has isolated proteoses which when injected into animals cause a marked increase in nitrogen elimination, presumably due to destruction of tissue proteins. He also observed an increased resistance of the animals after repeated injections. It is well-known that the characteristic rise of temperature following the injection of tuberculin into tuberculous individuals is also produced if minute quantities of proteose solutions are injected in place of tuberculin. The value of Commercial Witte's peptone probably lies in its containing, not peptone, but higher protein products. Clark[74] finds

most of the toxicity of the 'peptones' to depend on the higher proteoses, but there is also an alcohol soluble toxic element believed to be distinct from histamine. This substance has been named 'vasodilatin' by Popielski[75] and has all the characteristics of Vaughan's protein poison. Auld[76] says that peptone interacts with the fluids and tissues of the body in the production of a poison which desensitises to a poison produced by antigen and antibody. The base histamine produces effects similar to peptone poisoning, and it has been suggested that the effects of non-specific protein are due to its containing histamine. Histamine was originally isolated by Barger and Dale[77] from ergot in 1910 and then from the intestines. Every known protein contains as one of its fractions, histidine; if a single CO_2 molecule is broken off from this histidine, this powerfully toxic substance, histamine is formed. This substance when liberated from the tissue cells can produce all the phenomena of allergy. Lewis[78] showed that intradermal injection of histamine could produce first a dilatation of capillaries, and later an increased permeability of these capillaries and a widespread dilatation of the surrounding arterioles; these are the phenomena exhibited in urticaria, which is an allergic disease. Histamine, when injected into

animals produces all the phenomena of anaphylactic shock and peptone shock, except that it does not produce the profound alteration in the coagulability of the blood; it kills guinea pigs by causing intense spasm of the bronchi, and rabbits by obstruction to the pulmonary circulation. When injected in very small doses into man, it causes dizziness, flushing of the skin, tachycardia and a marked fall in blood pressure and it also acts as a strong stimulant to the gastric glands.[79] Commercial Witte's peptone contains measurable amounts of histamine but Hanke and Koessler[80] have shown that 'fibrin-peptone' apparently free from histamine, produces a typical peptone shock. The work of Lewis[81] shows that in all anaphylactic and anaphylactoid conditions, a fundamental factor is the liberation of an H substance, which is either histamine or a histamine-like body. Where precisely does the formation of this histamine or H substance take place? Weil[82] observed phenomena which led him to conclude that it is in the body cells that the reaction takes place. This is supported by Dale's reaction in which the uterus of the sensitised animal is carefully freed from blood and suspended in a bath of Ringer's solution; the addition of a minute trace of the substance to which the animal is

sensitised will cause an immediate contraction of the uterine muscle. If this is so, it is likely that the union of antigen and antibody act like any other injurious stimulus by releasing it from the tissue cells or from the liver. It is of interest that the histamine theory was evoked to explain the shock following severe crushing wounds. Can the problem be carried further to explain the relation between histamine and allergy? The discovery of histaminase, as mentioned previously, suggests the theory that the lack of this enzyme in the allergic individual leads to the setting free of histamine. If this is so, one would expect to find abnormal amounts of protein disintegration in the blood or urine of allergic subjects. Oriel[83] has claimed that he can demonstrate an abnormal protein derivative in the urine of such patients and he has given the name 'proteose' to this. Barber[84] believes that injections of autogenous urinary proteose are specific in conditions such as chronic urticaria, angio-neurotic oedema, eczema, prurigo, dermatitis herpetiformis and psoriasis. However the 'specificity' has been questioned by Lyon, Percival and Stewart[85], who say that the significance of this substance must be interpreted with caution.

Thus, it is fairly easy to understand why many different procedures, all tending to introduce into

the blood products of protein breakdown should have a similar pharmacological effect. The beneficial effects from this therapy are more difficult to understand. Some observers stated that this therapy establishes a state of vagotonia, a term introduced by Eppinger and Hess[86] to a condition suggesting excitability of the vagus nerve. Garrelon and Sartenoise[87] published results showing the presence of haemoclasia - that condition described by Widal, consisting of a reduction in the refractive index of the blood, increased coagulability and a leucopenia - in cases with signs of vagotonia. Pagniez[88] produced a leucopenia by stimulation of the vagus. It is interesting in this connection to note that asthma, an allergic disease, is probably due to the action of a foreign protein circulating in the blood, causing an irritable condition of the vagus nerve. Thus, there is the view that the asthmatic is a vagotonic and is liable to other manifestations of vagotonia. Weichardt[89] has come to the conclusion that in non-specific therapy all the cells are stimulated to greater activity in the production of either specific substances antibacterial in character or merely increase the general resistance to intoxication by speeding up the mechanism of detoxication by either forming conjugate proteins from the more complex

protein molecules or by breaking down the toxic portions of the protein to amino-acids. He calls his theory 'omnicellular plasma activation'; in his view, the leucocytosis, the increase in enzymes and antibodies indicate a general rather than a localised stimulation of some particular kind of tissue. Opposed to this view is that of Döllken[90], who has suggested that certain organs are stimulated by different agents to a greater degree than others, these being the liver, spleen, kidney and bone-marrow; a decided effect is also obtained on joints, the tissues of the eye and some of the glands. The nervous system can play no very great part in the reaction, for fatal shock can be produced when the central nervous system is completely cut off. The nervous system takes its part in this omnicellular reaction, even if it is not a productive part.

Physico-chemical Explanation:

Many support the idea that a change in the degree of dispersion of the blood colloids may be the fundamental factor[91]. The injections bring about a less dispersed state, affecting not only the serum proteins but also the serum lipoids, and a train of events is inaugurated when the equilibrium of some of the delicate serum balances is disturbed, all of which

tend towards a condition favourable to recovery. From the studies of Bäehr and Pick[92] it seems most probable that the toxicity of protein preparations depends to a large extent on the presence or absence of the cyclic or ring compounds in the protein molecule and perhaps also the size of the colloidal aggregate is of importance in determining the reaction after intravenous injection.

Inter-relations between Nervous and Chemical Mechanisms.

Dale[93] recently discovered that adrenaline directly antagonises histamine and this explains why adrenaline is the most effective treatment in an allergic crisis for it both neutralises histamine, which presumably acts by stimulating the vagus nerve, and stimulates the sympathetic nerves to plain muscles, such as those of the bronchi, intestines and uterus.

The Effect of Non-specific Protein on Animal Infection.

This therapy does not lend itself readily to experimental investigation in the laboratory. Acute infections in laboratory animals are usually too acute and too short to render possible a trial of this treatment. Chronic infections, with the exception of tuberculosis are not easily induced. In pigeons it has been found that a relative immunity to

b. avisepticus has resulted from injection of b. coli vaccine[94]. V. Hutyra & Muninger[95] showed that no protection was afforded rabbits inoculated with anthrax by treatment with normal horse serum. Bingel[96] treated 471 cases of diphtheria with diphtheria antitoxin and 466 cases with normal horse serum. As far as could be judged the two series showed no difference in the mortality. This has not been confirmed by other observers, e.g. Calhoun[97] found only a slight protection conferred on guinea pigs by injection with normal horse serum. On the whole, laboratory evidence fails to confirm clinical evidence.

Whatever may be the exact explanation of protein reactions, they appear to be of undoubted value in several conditions in which there appears to be a balance between the antigen and the bodily defence. The reaction may be looked upon as an exaggeration of the normal defence mechanism against foreign protein. Each animal has to build up its own characteristics and special tissues from the large number of amino-acids which result from the disintegration of food proteins. Any attempt to alter or prevent this normal mechanism, as by inhalation, ingestion, absorption from skin, or by injection of a protein, foreign to the particular animal, results in an attempt to get rid of such protein. The greater

the departure from normal the protein is likely to produce, the greater the reaction produced and vice-versa.

SECTION IV.

There are many methods of inducing protein shock. Those in common use may be classified as follows:

1. Proteins, e.g. casein, which is the principal albuminoid constituent of milk and is present in solution in the aqueous portion of the milk as an alkali-albuminate. It is precipitated by dilute acids and also by the action of rennet ferment. Purified casein is injected intramuscularly or intravenously to produce the effects of a foreign protein. A detoxicated milk protein, named aolan, first prepared by Biersdorf, may be used as an intramuscular injection in doses of 5 c.c. to produce a similar effect. Caseosan and lactin are similar preparations from milk.

2. The cleavage products of proteins, i.e. the substances produced from proteins as naturally occurs in the process of digestion, or which may be artificially prepared by the action of dilute acids or alkali, e.g. proteoses, deutero-albumoses and peptone. The former two are prepared from a solution of egg-albumin and are injected into the body intramuscularly or intravenously. A 4% solution of proteose in

doses of 2 c.c. intravenously has been used successfully in the treatment of chronic arthritis.[98] Peptone is a whitish powder, prepared from meat, which is peptonised either by acidulation and heat under pressure or by artificial digestion with pepsin or trypsin, and freed from saline matter. Commercial peptone such as Armour's 'ordinary' peptone or Witte's is used. The strength of the formed solution is 5% and the latter 2%. Both are given intravenously. The initial dose is 0.3 c.c. and is given at body temperature. Peptone has its greatest value in the treatment of cases of rheumatoid arthritis and asthma although it has been used with success in skin disease, e.g. pemphigus chronicus; in this latter instance, the solution strength is greater than usual, viz. $33\frac{1}{3}\%$ and it is injected intradermally.

3. Fluids containing proteins, e.g. (a) milk, blood or serum from the human being, the ox, the cow or other animals, (b) antitoxic serum, e.g. anti-scarlatinal, antidiphtheritic, antistreptococcal, usually obtained from the horse or cow, (c) body fluids, e.g. pleural effusions, joint fluid, cerebro-spinal fluid. Milk is injected intramuscularly in doses of 5 c.c., usually at intervals of five to seven days. Blood or serum is taken from the same individual, a second individual or from an animal,

i.e. autohaemotherapy, autoserotherapy, heterohaemotherapy, heteroserotherapy are practised. The dose of these is 10 c.c. injected intramuscularly, repeated at intervals according to the effects on the patient. Of the body fluids the most commonly used is the fluid from a case of pleural effusion. The fluid is injected intramuscularly in doses of 5-10 c.c. Marked improvement has resulted in the treatment of pemphigus by the subcutaneous injection of fluid from the patient's own blisters. Antiscarlatinal, antidiphtheritic and antistreptococcal sera may be used in diseases, other than those in which they are specifically used for their protein effects. They may be injected intramuscularly or intravenously, e.g. diphtheria antitoxin has been injected intramuscularly in the treatment of erysipelas.

4. Vaccines, e.g. streptococcal, staphylococcal, typhoid. The anti-typhoid paratyphoid vaccine commonly called T.A.B. vaccine is commonly used in the initial doses of 50-100 million bacilli intravenously, in the treatment of rheumatoid arthritis. Similarly, tuberculin in the form of old tuberculin, in an initial dose of 0.1 c.c. of a weak dilution, may be injected subcutaneously in cases of asthma.

5. Coley's Fluid. Preparations containing products of protein breakdown, e.g. human or animal

tissue extracts, e.g. an extract of cartilage is used in Germany according to the instruction of Heilner[99] and is called 'Sanarthrit'. Spleen extracts, polyglandular extracts, skin scale extracts, tumour extracts may all be included in this category.

6. Chemical substances, e.g. nuclein, sodium nucleinate, tallianine, which when injected intramuscularly produce changes in the body similar to those induced by bacterial protein. Other drugs, e.g. turpentine, sometimes injected intramuscularly in cases of skin disease or quinine, injected intramuscularly in cases of puerperal sepsis, act in a different way. They produce a 'fixation abscess', causing a breaking down of tissue and by absorption a protein effect.

7. Artificially induced diseases, e.g. malaria in cases of general paralysis insane and relapsing fever in the same disease. The former disease is transmitted to the patient by direct infection from a mosquito bite or indirectly by transference of blood from a patient known to be suffering from benign tertian malaria.

Bier[100] is of the opinion that any measure which causes protein breakdown causes results similar to those following the injection of protein. According to this view, there should be included under the same heading:

a. Intravenous injections which alter the blood protein, e.g. sodium thiosulphate, calcium chloride.

b. X-rays which destroy blood cells. Treatment by cautery, diathermy, radium, CO_2 snow and helio-therapy.

(i) The proteins used in the present investigation were milk, T.A.B. vaccine, tuberculin, and the proteins of the plasmodium malariae. Milk is one of the least injurious protein mixtures to use, it is always at hand, is easy to administer and easy to sterilise; these actions are not severe and the patient is as a rule not unduly upset. I prefer this non-specific protein to specific protein in the treatment of cases of erysipelas, because I have seen several alarming results from the use of erysipelas antitoxin and serum. By the latter mode of therapy, there is always the immediate risk of anaphylactic shock and the later occurrence of serum sickness. I have not found these to occur with the use of milk. The latter is preferably given intra-muscularly because the reaction after intravenous injection is unnecessarily severe and is not so convenient or easy as intramuscular injection. The dose used in this instance was 5 c.c. and this amount was sterilised prior to injection by boiling for five minutes. The injections were given at intervals of two days and

the number given varied according to the effect on the disease and the effect on the patient. The average number was five injections.

Anti-typhoid-paratyphoid vaccine was used in the second series of cases because the literature shows that this is perhaps the most successful protein used in this disease. It is preferable to specific vaccine therapy, i.e. vaccines prepared from germs found in some focus of infection - these latter do not always succeed in improving the disease, and the body defence is not stimulated to such a degree as by non-specific protein. Fresh vaccine was always used and in 1 c.c. there were 500 million typhoid bacilli, 250 million paratyphoid A and 250 million paratyphoid B. The injections were given intravenously; subcutaneous injection is apt to be followed by a severe local reaction without any great general upset of the patient. The dosage was 100 million total organisms, increased by a similar dose every five days. The literature on the subject of dosage varies, e.g. Cecil[101] recommends 30 to 100 millions, Campbell[102] 125-200 millions. Miller & Lusk[103] gave 150 millions and then reduced the dose to 75 millions. Cowie[104] seldom gives a dose of less than 500 millions and has given this dose in children with no untoward result.

In the treatment of asthma, specific means of desensitisation have been used. By skin tests it is possible to find the protein which is responsible for the sensitisation of the particular individual. The injection of a small dose of the dilution of the offending protein at intervals sometimes will benefit these cases; on the other hand it often fails. The above tests have the disadvantage in that they are not always easy to carry out and it takes a considerable amount of time to complete them. If the same or better results can be procured by non-specific protein, without the previous testing of the skin, then the advantage lies with the latter. According to many observers, the latter form of therapy is preferable to specific protein. Old tuberculin has been used in the treatment of the cases recorded here. The material for injection consisted of dilutions of old tuberculin contained in rubber-capped bottles, the dilutions ranging from 1 in 1,000,000 to 1 in 100. The initial dose was 0.1 c.c. of the former dilution given subcutaneously and the amount injected was gradually increased every six days, e.g. 0.2, 0.4, 0.6 c.c. proceeding thence to 0.1 c.c. of the dilution immediately stronger. The maximum dose used was 0.2 c.c. of 1/1000 dilution.

Malarial therapy was used in the series of cases

of general paralysis of the insane. Other protein methods have been used in the treatment of this condition, particularly T.A.B. vaccine, but the latter has the disadvantage in that it requires to be injected at intervals and also that the reaction following its injection is not sufficiently prolonged to be of any great benefit. Malarial therapy produces a prolonged reaction and it can be readily controlled. Inoculation with malaria may be carried out directly from one patient to another, or the malarial blood can be citrated or defibrinised and injected later on. More recently, infected mosquitoes have been utilised to inoculate the patient. In the cases here recorded the inoculation was done directly from one patient to another and the blood injected either deep subcutaneously or intravenously in doses of 5.c.c.

(ii) The patient were carefully selected. The ages ranged from twenty to sixty years and they were of both sexes. Old age and infancy are not to be taken as contra-indications; I did not have the opportunity of treating patients at these ages. Tuberculosis is an absolute contra-indication,because a latent area of disease may be stirred to fresh activity by any violent reaction produced. Cases of chronic myocardial change and arterio-sclerosis were

not considered suitable. Cases of valvular disease fully compensated, suffered no ill-effects. Alcoholics were not treated in this way because of the possibility of the development of delirium tremens. If the patient had albuminuria, renal function tests were used prior to deciding on this therapy. If these tests were satisfactory, albuminuria was not considered a contra-indication although Campbell[102] reports a case of haematuria in a patient who had albuminuria prior to the injection. Mental instability was considered a definite indication for the treatment of the cases of general paralysis insane.

(iii) The cases of erysipelas were treated in bed in an isolation ward. The diet was light and consisted of milk, milk puddings and beef tea. Fluids were given ad lib. The bowels were freely opened at the beginning of the disease by giving hydrarg subchlor. gr.iii and following this up in four hours by giving a saline aperient. No other drugs were given by mouth and as an external application, fomentations four hourly were used.

The ~~second~~ third series of cases was treated in bed. Aperients were given twenty-four hours prior to injection and a light diet given for a similar period.

For the disease itself, various methods had been previously tried - removal of foci of infection, passive movement, massage, radiant heat, hot air baths and drugs such as potassium iodide and guaicol carbonate.

The asthmatic patients were at first treated in bed. They were kept in hospital for a month and later observed and treated as out-patients. Beyond attention to the bowels, no special pre-injection treatment was given. For the asthma itself, sources of reflex irritation such as nasal disorders, urethral or uterine disease were sought for and removed. Skin tests to detect any particular sensitiveness were not used, nor were vaccines made from the predominant organism in the sputum.

Malarial therapy was induced with the patient in bed. The same attention as to diet and bowels was given as in the previous cases. Specific therapy in the form of tryparsamide injected intravenously was given to each patient. Twenty-four grams of this drug, given over a period of three months constituted a course. In addition, pot. iodid. gr. ½ t.i.d. was given during the same period.

(iv) Technique. For the milk injections, a 10 c.cm. record syringe, sterilised by leaving in spirit for twenty-four hours was used. A sterile

needle, two inches long, with a flat straight point, was used. The needle was attached to the syringe, 5 c.c. of milk, previously sterilised, drawn into the syringe; the needle was next detached from the syringe and thrust into the buttock at a point on the outer quadrant, slightly above the level of the upper point of the natal cleft. The barrel of the syringe was refixed and the injection made.

For T.A.B. injections a similar syringe was necessary. The needle, however, was smaller, of finer bore, and had a sickle-shaped point, which enabled it to pass through the vein wall without any great pressure. The requisite dosage of the vaccine was drawn up into the syringe and this was diluted with normal saline up to 5 c.c. A suitable vein at the elbow, which had previously been made to stand out by application of a tourniquet, was chosen and the injection given slowly.

The tuberculin injections were given by a 1 c.c. hypodermic syringe with a fine hypodermic needle. The desired amount of vaccine was drawn up and without dilution with saline, was injected under the skin of the forearm or arm.

Five cubic centimetres of blood, from a patient suffering from benign tertian malaria, was withdrawn from a vein into a 10 c.c. record syringe. The

malarial blood was then transferred directly into a suitable vein of the patient to be inoculated, or having exchanged the intravenous needle for a longer needle and one of wider bore, the blood was injected deep subcutaneously between the scapulae.

(v) The patients were treated in bed following the injection, although this was not absolutely necessary in the case of those treated by tuberculin; these latter were subsequently treated as out-patients. Light diet was continued for a further period of forty-eight hours in all cases and the patient carefully observed for any local or general sign of reaction. The pulse and temperature were recorded every four hours. Those patients treated by malarial therapy were allowed to have twelve pyrexial attacks and the disease subsequently controlled by the administration of tabloids of quinin bihydrochlor. gr.ẋ morning and evening for five days and then gr. ẋ daily for a further three days.

(vi) After the intramuscular injection of milk the patient always complained of discomfort at the site of injection. Twelve hours later he would complain of headache and malaise; the temperature was usually raised by one degree and the pulse rate increased by ten beats per minute. Twenty-four hours

later the local and general symptoms had disappeared; the pulse was at least ten beats per minute slower and the temperature was lower by two degrees. The effect on the disease itself was at first to increase the pain and discomfort caused by it; the first injection did not arrest the progress of the disease, which in fact usually continued to spread for a further period of forty-eight hours.

With T.A.B. vaccine the reactions were severe. A sharp febrile reaction was obtained in all cases. The symptoms observed were similar to those experienced in malarial chill, but not so severe. The patient at first complained of the cold shortly after injection; in fifteen - sixty minutes he had a rigor. There was then a period of warmth in which the temperature reached a height of 104°; I did not observe a temperature higher than 104.2°F. F. Cecil[101] has recorded a temperature of 107°. In this stage there was intense headache, nausea and vomiting. There next followed a sweating period in which the patient was bathed in profuse sweat. The joint pains were increased for a period of twenty-four hours, but these soon disappeared and were followed by a feeling of comfort and well-being. The temperature returned to normal within thirty-six hours. Some mental excitement and confusion did occur in three cases, but

no other complications have attended the course of injections.

The dosage of tuberculin was so graduated that all local and focal reactions were avoided. A general reaction in the form of headache, malaise and a temperature of 99° was sometimes observed four to six hours after injection, but this disappeared within twenty-four hours.

The pyrexial attacks after injection of malarial blood commenced within a varying period of injection. After intravenous injection they usually appeared within a period of eight days, but after deep subcutaneous injection the rigors were delayed as long as three weeks on two occasions. During this interval the patient complained of headache and within twenty-four hours of injection the temperature was raised to 99° F. The rigor itself was always preceded by headache and malaise and the fever observed was always of the quotidian type. The pyrexial attack showed the three stages found in a malarial paroxysm - a cold stage, when the patient shivered violently and goose-skin appeared. The hot stage followed, accompanied by high temperature, often 105° F. The skin was hot and red, vomiting increased and there was sometimes delirium. The sweating stage next occurred. The pulse and temperature fell gradually to the normal.

Herpes labialis occurred in the majority of cases. Complications, such as jaundice and hyperpyrexia, occurred in three cases. Signs of cardiac failure, requiring the use of cardiac stimulants were seen in two cases. Mental symptoms were aggravated in five cases and in the remainder, the patient became quieter and more easily managed.

It is necessary to adopt a standard by which to estimate results and I have used the following classification. This latter is difficult in erysipelas, which is a self-limited disease.

Erysipelas.

(a) Cures were those cases where all signs and symptoms had disappeared within seven days of the origin of the disease.

(b) Failures - where the disease continued for a longer period of seven days or was attended by complications.

Chronic Arthritis.

(a) Cures when the patient was sufficiently well to leave hospital and resume his or her occupation.

(b) Satisfactory if the condition were sufficiently alleviated to allow the patient to get about.

(c) Failures were those cases where there was no improvement in the condition.

Asthma.

(a) Satisfactory result if at the end of twelve months the patient has no asthmatic attacks.

(b) Failures when at the end of twelve months there is no diminution in the number of attacks.

(c) Improved when there is a diminution in the number of attacks.

General Paralysis of the Insane.

(a) Satisfactory if the patient could resume his former occupation.

(b) Poor result if the mental and physical condition were improved but not sufficiently to allow him to resume his occupation.

(c) Failure, when there was no appreciable difference in the mental and physical condition and when he still required to be detained in an institution.

SECTION V.

Case Records

Erysipelas.

The diagnosis was made by the history and clinical examination of the patient. The disease was of sudden onset with headache, vomiting and very often with a rigor. The temperature was 103° or higher and a sharp, red, raised patch appeared on the skin of the affected area. This rapidly spread in all directions and superficial blebs appeared on the surface. To ensure a correct diagnosis, a case was not accepted for this investigation unless vesicles in addition to the other signs were present. The cases treated were of one of three types:-

(a) Idiopathic, that is there was no known antecedent cause.

(b) Traumatic, where the infection commenced in a breach of the skin.

In both these types the infection remained localised.

(c) Erysipelas migrans, where the inflammation healed in one part and spread in another area of the body.

TABLE I.

Cases Treated:

No.	Age	Sex	Site of Erysipelas	Type	No. of attacks	Result
1	25	M	Face	Idiopathic	2	Cure
2	40	F	"	Traumatic	2	Cure
3	30	M	"	Idiopathic	2	Cure
4	22	F	"	Idiopathic	2	Cure
5	33	F	"	Idiopathic	3	Cure
6	42	M	"	Traumatic	First	Cure
7	40	M	"	Idiopathic	First	Cure
8	29	M	"	"	2	Cure
9	56	M	"	"	2	Cure
10	52	M	"	"	2	Cure
11	50	M	Leg	Migrans	First	Cure
12	21	M	"	"	"	Cure
13	34	M	Abdominal Wall	"	"	Cure
14	33	M	Chest Wall	"	"	Cure
15	35	F	Right Breast	"	"	Failure
16	45	M	Both legs	"	"	Failure
17	41	M	Abdominal Wall	"	"	Failure
18	38	M	Chest	"	"	Cure
19	36	F	Chest	"	"	Cure
20	34	F	Right Breast	"	"	Failure

Thus, of twenty cases treated, the infection was on the face in ten cases and in other parts of the body in the remaining cases. Ten cases were of the spreading type and ten cases of the simple non-spreading type. Twelve cases were primary, seven patients were experiencing their second attack of erysipelas and one was having his third. Sixteen cures resulted and failures occurred in four cases of the 'migrans' type. A persistent temperature after the seventh day was the cause of failure in these latter.

At the end of twelve months, patients eight and nine in the above group had a recurrence of facial erysipelas, but the remaining patients were free from infection at the end of this period.

The results may be compared with a series of twenty cases admitted to Stepping Hill Hospital during the year 1932 and treated by fomentations or ointments locally, by tr. ferri chlorid. internally and by injections of polyvalent antistreptococcus serum or erysipelas antitoxin. No milk injections were given.

TABLE II.

No.	Age	Sex	Site of Erysipelas	Type	No. of attacks	Result
1	43	F	Face	Idiopathic	one	Cure
2	52	F	"	"	"	"
3	60	F	"	"	"	"
4	49	M	"	"	"	"
5	62	F	"	"	"	"
6	65	F	"	"	"	"
7	48	M	"	"	"	"
8	51	M	"	"	second	Failure
9	46	M	"	"	one	Cure
10	39	M	"	"	second	Failure
11	38	M	"	"	one	"
12	42	M	"	Migrans	"	Cure
13	43	M	"	"	"	Failure
14	45	M	Abdomen	"	"	"
15	46	M	Chest	"	"	Cure
16	52	M	Legs	"	"	"
17	50	M	Face	"	second	Failure
18	49	M	"	"	one	Cure
19	48	M	"	"	second	Failure
20	47	M	Chest	"	one	Cure

Thus eleven cases were idiopathic and nine cases of the spreading type. Four patients were having

their second attack. There were seven failures and it will be noted that three of these were of the 'migrans' type and four were recurrent cases. A comparison of the results in the two groups of cases may be made in the following tables.

A.

Table	Primary Attacks	Cures	Failures
1	12	8	4
2	16	13	3

B.

Table	Second or Third Attack	Cures	Failures
1	8	8	-
2	4	-	4

C.

Table	Cases of 'Migrans' Type	Cures	Failures	Average duration of stay in hospital.
1	10	6	4	16
2	9	5	4	21

It will thus be seen that in primary attacks of erysipelas there is very little difference between the results in cases treated by milk injections and in those treated by other means. In cases where there had been two or more attacks, better results were obtained in those treated by milk. Table C. shows that there is very little to chose between the two treatments in cases of erysipelas migrans, as far as actual cure and failure figures go. It will be noted,

however, that the average duration of stay in hospital is shorter in those treated by milk. A further point may be made that the cause of failure in Table I was the persistence of the temperature after the seventh day, with no complications present, while in Table II these failures were due to cellulitis and local abscess formation.

Discussion: Most primary cases of erysipelas get well spontaneously and in the above series of sixteen cases, thirteen recovered within seven days without the exhibition of any special local or general treatment. On the other hand, a recurrent case does not recover so spontaneously and such a case benefits by milk injections. Cases of erysipelas migrans are the ones which most often show complications; these can be reduced to a minimum by non-specific protein. By means of the latter also, the length of the disease can be shortened. Thus, milk injections should not be used as a routine but confined to the above special type of case. Many varieties of protein have been tried in erysipelas, e.g. auto-blood and a case of recovery has been recorded in an infant after injections of the father's blood. Antidiphtheritic serum has been used with excellent results. Milk and its derivatives, e.g. aolan, caseosan, have been used more frequently than

other proteins. Some observers stress the benefit of injecting the milk near or round the lesion; this latter method, however, is unnecessarily severe and as good results can be obtained by intramuscular injections of milk. The latter have the advantage in that they are easy to administer, they do not upset the patient unduly and do not result in local abscess formation. The contra-indications to its use are those of non-specific therapy in general, namely alcoholic patients and those with chronic myocardial changes and advanced arterio-sclerosis.

The exact action of milk is unknown. It is obvious that it does not act by producing fever, because its action is to reduce the temperature. This reduction of temperature is unlikely, as has been suggested, to be due to a paralysis of the heat regulating centre in the medulla. The beneficial reaction is not due to leucocytosis for milk injections cause little or no increase in the white cell count. Larson's theory that milk causes the specific antibodies produced by the infection to be thrown into the blood stream, seems the most likely explanation.

Asthma.

The diagnosis rested on the observation of the asthmatic attack in hospital. In fifteen cases the attacks occurred at night and in five they occurred during the day. The classical picture was presented. The patient had a feeling of intense dyspnoea; he felt as if there were not sufficient air in the ward and he either stood out of bed or grasped the bed in such a way that he might breathe the more easily. There was an anxious expression on the face, often accompanied by cyanosis. Expiration was prolonged and the breathing of a wheezing type. The paroxysm was relieved by a bout of coughing and expectoration of a frothy sputum.

There were two types of case treated and in neither type was there clinical or other evidence of tuberculosis.

Type A. Pure asthma with no secondary changes in chest.

Type B. Asthma complicated by bronchitis, emphysema and myocardial change.

Cases:

No.	Age	Sex	Duration of Disease	Type of Asthma	Average No. of Attacks per month	Result of 6 months Treatment
1	21	M	5 years	B	4	Satisfactory
2	25	M	2 "	A	5	"
3	30	M	4 "	A	5	"
4	21	M	6 "	B	3	"
5	23	M	10 "	B	6	Improved
6	25	F	5 "	A	7	"
7	30	M	3 "	A	7	Satisfactory
8	36	F	6 "	B	4	Failure
9	30	M	3 "	A	5	"
10	32	M	9 "	B	6	"
11	30	M	2 "	A	3	Satisfactory
12	31	F	1 "	A	1	"
13	45	M	12 "	B	3	Failure
14	50	F	10 "	B	5	"
15	52	F	10 "	B	7	"
16	46	M	3 "	A	9	"
17	41	M	4 "	A	10	Improved
18	33	M	6 "	B	3	"
19	30	M	5 "	B	4	Satisfactory
20	22	M	8 "	B	2	Improved

Thus twenty cases were treated, five females and fifteen males. At the end of six months' treatment, eight patients were free from asthmatic attacks,

five improved and seven showed no improvement. The relation between the result of treatment and type of asthma is shown in the following table:

Type of Case	Satisfactory	Improvement	Failure
A	5	2	2
B	3	3	5

The satisfactory results were obtained in the cases of asthma of shorter duration. The dosage of tuberculin would appear to have no relation to the satisfactory cases as in the tables below:

No.	Maximum Dose of Tuberculin
	Satisfactory Cases
1	0.2 c.c. of 1/1000 dilution
2	0.2 c.c. of 1/10,000 "
3	0.4 c.c. of 1/10,000 "
4	0.8 c.c. of 1/100,000 "
7	0.2 c.c. of 1/1000 "
11	0.6 c.c. of 1/10,000 "
12	0.4 c.c. of 1/10,000 "
19	0.2 c.c. of 1/1000 "
	Improved Cases
5	0.2 c.c. of 1/1000 "
6	0.4 c.c. of 1/10,000 "
17	0.6 c.c. of 1/10,000 "
18	0.4 c.c. of 1/10,000 "

No.	Maximum Dose of Tuberculin	
	Improved Cases (contd.)	
20	0.4 c.c. of 1/10,000 dilution	
	Failures	
8	0.6 c.c. of 1/10,000	"
9	0.2 c.c. of 1/1000	"
10	0.4 c.c. of 1/10,000	"
13	0.4 c.c. of 1/10,000	"
14	0.6 c.c. of 1/10,000	"
15	0.8 c.c. of 1/100,000	"
16	0.2 c.c. of 1/1000	"

At the end of a further period of six months' treatment, using a similar dosage, cases 5 and 7 relapsed so that two failures have to be added to the previous list. The final results may thus be tabulated:

Type of Case	Satisfactory	Improvement	Failures
A	5	1	3
B	3	2	6

Discussion: The treatment by tuberculin was originally introduced by Professor Van Teeuwen for the treatment of asthmatic patients who gave a positive reaction to the tuberculin skin test. It has since been shown by other writers on the subject, particularly Simpson Stone and Maxwell, that tuberculin acts

equally as well in a patient with a negative skin reaction. On that account, the usual preliminary skin test was dispensed with in this investigation. None of the cases treated showed any evidence of tuberculosis, so that the treatment must be regarded as a non-specific one. The rationale of the treatment is not clear; the temperature can have very little relation to the results achieved, because very rarely is the temperature raised, and, if raised, not above 99° F. Perhaps tuberculin acts as a general desensitising agent, that is, by removing or fixing the particular offending protein. It has been suggested that the psychological effect of injections is a potent factor; this may be so in a nervous type of patient but in none of the above recorded cases was there any evidence of neurosis.

From these results it is difficult to point out the exact case in which tuberculin is most suitable; it would appear to be almost as successful in cases of asthma complicated by bronchitis as in the primary allergic cases of the disease. It is not suggested that this treatment should be used as a routine; all known methods of investigation and treatment should first be tried. Any abnormal nasal condition should be corrected, as also should any demonstrable abnormality of the alimentary tract; the patient's

surroundings should be investigated as to whether a change of occupation or habitude would be of benefit; skin tests for the presence of any particular foreign protein should be tried, and subsequent desensitisation by suitable injections of the specific protein carried out. If these fail, then tuberculin treatment may be resorted to. Treatment of under six months' duration is of little value; and if the patient has benefited by the first course, he will benefit probably to a greater degree by the second. Old tuberculin is more successful than tuberculin A.F. (albumose-free) and this is probably due to the presence of albumose.

Arthritis.

To facilitate the analysis of this investigation of the effect of T.A.B. vaccine on rheumatoid arthritis, it is necessary to have some scheme of classification, and for this purpose I have used the scheme advised by Pringle & Miller[105]. They classify arthritis in seven groups - infective, metabolic, neurotrophic, traumatic, degenerative, toxic and periarticular fibrositis. It is this degenerative group that interests us here; included in it are:

A. The ordinary chronic form of rheumatoid arthritis in which the joints are involved symmetrically, especially the metacarpo-phalangeal and inter-phalangeal joints. The joints are stiff and there is deformity at the wrist, caused by flexion at the metacarpo-phalangeal joints, over-extension at the first phalangeal joints, flexion at the second phalangeal joints and deviation of the fingers to the ulnar side.

B. The type characterised by osteophytes or Heberden's nodes, and

C. The monoarticular form of the disease known as morbus coxae senilis. The cases treated belonged to one of these groups.

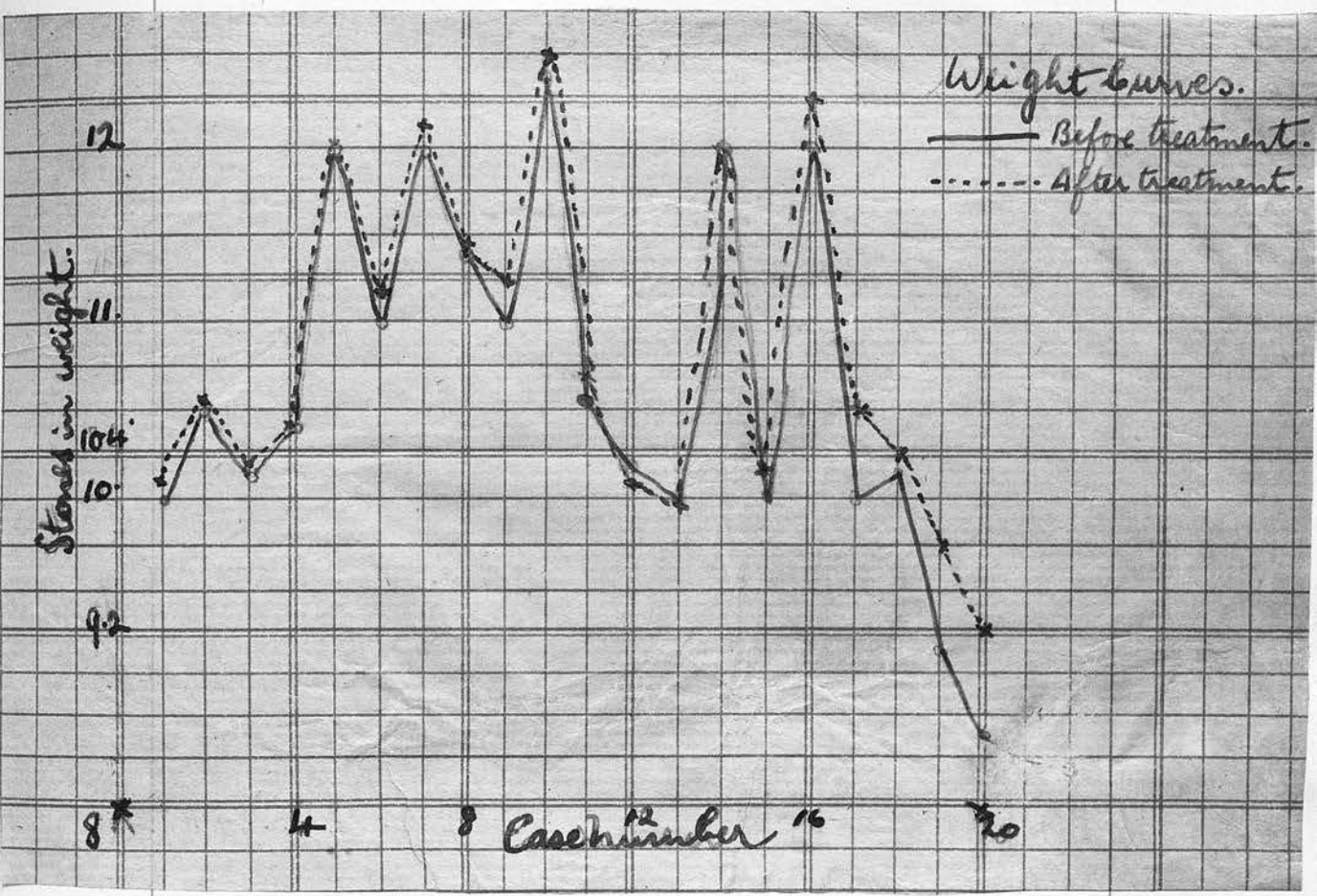
No.	Age	Sex	Joints Affected	Type of Disease	Result
1	35	F	Both wrists	B	Satisfactory
2	38	F	Right wrist and ankle	B	"
3	42	F	Both wrists	B	"
4	43	F	Both wrists	A	"
5	51	M	Spine	C	Failure
6	49	F	Both ankles	A	Cured
7	60	F	Right knee	C	Failure
8	58	M	Right hip	C	"
9	42	F	Left shoulder	C	"
10	51	M	Right hip	C	"
11	50	M	Right hip and right knee	A	Cured
12	46	F	Right shoulder	C	Failure
13	43	F	Right hip	C	"
14	60	F	Right hip	C	"
15	58	F	Right shoulder	C	Cured
16	42	F	Both wrists	A	"
17	36	F	Left ankle	A	"
18	35	F	Both wrists	A	"
19	30	F	Both wrists	A	Satisfactory
20	28	F	Both wrists	A	Cured

Thus twenty cases were treated with T.A.B. vaccine, eight cases were in Group A, that is the type associated with synovial changes and deformity

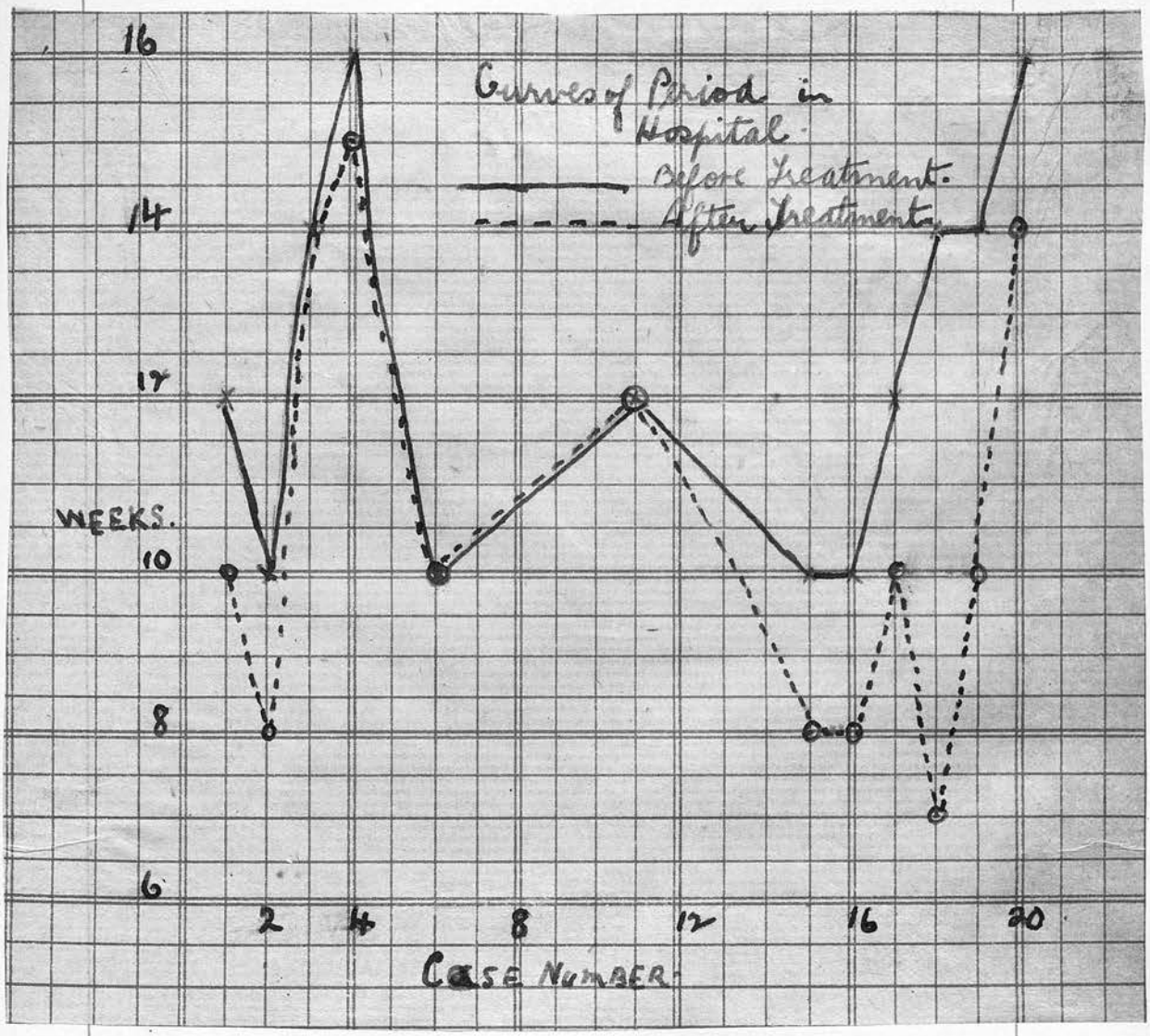
of the affected joint, three in Group B, the type associated with osteophytes and the remaining nine cases were of the osteo-arthritic type. The results in the different groups will be seen in the following table:

Group	Cures	Satisfactory	Failures
A	6	2	-
B	-	3	-
C	-	-	9

Thus it will be noted that all of the cures belong to Group A and all of the failures to Group C. Although nine cases showed no change in the joint condition it does not follow that they did not participate in the feeling of comfort and well-being generally experienced twenty-four hours after injection. The effect on the general condition may be adjudged by the weight curves, before and after treatment.



A comparison between this and other forms of treatment may be made by a study of the graphs showing the period in hospital before and after injection of T.A.B. vaccine:



The relation between the results and the number of injections is shown in the table below:

Result	Average No. of injections
Cured	9
Satisfactory	12
Failure	12

This would tend to show that the number of injections had no relation to the result obtained. The final dose of vaccine in all cases was 500 million organisms and no course of treatment was considered complete until this dose had been reached by gradual stages.

Subsequent history of cases twelve months after initial injection.

In the six cases, previously recorded as cures, there were no relapses, but of the five satisfactory cases, three relapsed. The nine cases in the failed group were given a second course of vaccine and the results at the end of twelve months are summarised in the following table:

Type of Disease	Cured	Satisfactory	Failure
A	6	2	-
B	-	3	-
C	-	3	6

Discussion: The beneficial results were for the most part obtained in those cases with synovial changes in the joints. These favourable cases were chiefly due to the focal reaction produced by the vaccine, causing an increase in the blood supply of the joint and followed by an absorption of inflammatory products. From this observation alone, it would not be rational to expect such beneficial results

in cases showing ~~long~~ bony changes, such as Heberden's nodes or osteo-arthritis; in none of the above cases was there any improvement to be observed in the bony condition by clinical or radiological examination. Nevertheless these latter cases are sometimes improved by this treatment and especially is this so if a second course of vaccine has been administered. If cases of arthritis differ in the functional results achieved, they all experience beneficial effects such as increased appetite, comfort and freedom from pain. These latter are probably to be explained by the general reaction produced, particularly the pyrexia, which results in an increased activity in the tissues and organs. The most desirable temperature, in my opinion, is one of 103° F or at the most 103.5° F; in one case the temperature was 104.2° F. but the effect was so severe that it took the patient three days to fully recover from headache and sickness. The more gradually the maximum dose of 500 million organisms is reached the less severe is the general reaction likely to be. The chief disadvantage of the treatment is this severe reaction, but apart from some mental confusion, no other untoward symptom is likely to follow its use. It is not indicated in every case of rheumatoid

arthritis, but in any case, which does not respond to climatic, dietic, medicinal and physical methods of treatment, the treatment suggested itself to me by reason of the non-success of the above methods in the cases recorded. The patients themselves must not be old and debilitated or suffer from myocardial or kidney disease.

General Paralysis of the Insane.

Diagnosis was founded on clinical symptoms and signs and verified by examination of blood and cerebro-spinal fluid. An average case showed tremulousness of the lips and facial muscles. The speech was slow and indistinct. The pupils were of the Argyll-Robertson type and there was a history of apoplectiform seizures. The gait was impaired and the patient had difficulty in walking up or down-stairs. The deep reflexes were exaggerated and there was incontinence of urine. There was marked mental excitement and physical restlessness with a periodic tendency to acute maniacal outbursts. Forgetfulness was common but delusions were infrequent being found in only two cases.

The blood Wassermann was strongly positive in seventeen cases, and weakly positive in three cases. The Wassermann reaction of the cerebro-spinal fluid was positive (xxx) in all cases. In all cases an examination of the C.S. fluid showed an increase in cells of the lymphocyte variety (average no. 20), an increase in the globulin and Lange's gold solution gave a paretic curve in every case.

	Number	Age Group	Sex of cases treated	
			M.	F.
	2	20-30	1	1
	3	30-40	3	-
	9	40-50	7	2
	6	50-60	5	1
Total	20		16	4

Previous Treatment: All these patients had been treated previously, on an average, for a period of three years, to the hilt of tolerance, with anti-syphilitic drugs.

Results of Treatment:

Age Group	A Satisfactory	B Poor	C Failure	Total
20-30	2	-	-	2
30-40	2	-	1	3
40-50	5	3	1	9
50-60	3	2	1	6
Totals	12	5	3	20

Thus twelve patients, at the end of treatment, were capable of resuming full wage-earning work, which was of a varied character - two were office clerks, two were motor drivers, two were engineers, one a farmer, three were housewives and two were miners. Five were improved but not sufficiently to resume their occupations and two showed no apparent improvement either

in the physical or mental condition, while one died during treatment. The effect of treatment in Group A was to make these patients appreciate the foolishness of their former optimisms. Judgment and insight were restored. Speech was clear and the memory good. Tremor was not observable, although slight twitching of the facial muscles was observed in three cases. Their irritability remained and was easily aroused to anger if argued with. Although they could carry out their work, they were more easily tired than previously.

In Group B, the physical state of the patients was poor. They remained thin, pale and in a state of debility, although their weight had been increased by a few pounds and their appetite was better. There also remained slowness of thought, a poor memory, dullness, apathy and lack of judgment; the restlessness and mental irritability were, however, not quite so marked.

In Group C, the patients remained as before, presenting gross clinical signs of general paralysis insane.

Changes in the Blood and C.S. Fluid: The Wassermann reaction of the cerebro-spinal fluid remained positive, while the blood Wassermann in the three cases previously noted as weakly positive

became negative. The fluid cell count in all cases was less with a corresponding diminution in the globulin. Lange's gold test showed a change in that the curve became luetic.

Subsequent observation of cases: All the cases with the exception of the two remaining in Group C were given the benefit of antisyphilitic treatment during the next twelve months. The observations during this period are summarised in the following table:

	Relapsed	Died
Group A.	3	-
Group B.	3	2
Group C.	-	2

The mortality will thus be observed to be one directly due to malarial therapy and four subsequent to the treatment. Six relapsed and thus nine cases remained in Group A, i.e. 45% of the patients were observed to have benefited by this treatment twelve months after its inception.

Discussion: Malarial therapy has thus, in a study of these cases, been found to increase the length of life, to render existence more natural and to produce improvement in the physical condition and mental state. The response to treatment in individual

cases has been noted to vary from a negative result to apparent complete recovery. It may be argued that these nine cases would have done just as well without malarial therapy, but this is unlikely, when it is remembered that the cases had been treated by routine antisyphilitic measures for three years previously, without showing any apparent improvement. The mortality may be pointed out against this treatment; in this series there was one case of doubtful propriety for this treatment. The risk was taken but the patient, a male, aged 59, died after the third rigor from cardiac failure. Four deaths occurred within six months of treatment and there does not appear to be any other explanation of this high death rate except that malaria itself is a potent factor. Yet, as ordinarily met with, benign tertian malaria is accounted a non-fatal and minor malady. The frequency of these early fatal issues does arrest attention, and one should bear in mind the contra-indications to the employment of malarial therapy, which are variously estimated - the chief of these are very old cachectic people and those suffering from advanced cardio-vascular disease.

Besides malaria, other forms of treatment for general paralysis have and are being made use of. These include, besides the usual antisyphilitic

remedies, mercurialised serum, salvarsanised serum and tryparsamide. Sodium nucleinate has been employed to produce leucocytosis and intramuscular injection of milk-protein shock - to produce fever; relapsing fever has also been tried. The evidence concerning these goes to show that none is superior or equal to malarial therapy.

Supplemental Treatment: The lack of permanence observed and of incomplete recovery recorded in several cases, suggested that malarial treatment, good though its unaided results may be, needed reinforcement. During the twelve months' observation of these cases, I used tryparsamide in doses of 2-3 grams, varying with the weight and age of the patient, given intravenously, at weekly intervals, over a period of three months, followed by one month's rest and then recommencing the treatment.

How does malaria act? Perhaps like any other fever, but with the advantage that it intermits and can be easily controlled by quinine. The blood is increased in activity and flow, the whole body is subjected to a kind of spring cleaning, the diseased tissue of the brain is dissolved and removed, and the spirochaetes, deprived of their defences, are rendered inactive and, temporarily at least, innocuous. This is precisely the effect following the injection

of any non-specific protein substance, and that is why I have included malarial therapy in these notes.

SUMMARY AND CONCLUSIONS

1. Twenty cases of erysipelas have been treated with milk injections, and a comparison made between these and twenty similar cases treated by other methods.

2. Milk injections have their greatest value in recurrent cases and in erysipelas 'migrans'.

3. Twenty cases of asthma were treated by injections of old tuberculin.

4. This treatment is safe and successful in cases of asthma which have failed to respond to other methods of treatment.

5. Twenty cases of rheumatoid arthritis were treated by injections of typhoid-paratyphoid vaccine.

6. This treatment must be used with care and judgment because it is apt to be followed by severe reactions.

7. Injection of vaccine should not be used as a routine measure in rheumatoid arthritis, but may be tried when other well-recognised forms of treatment have failed.

8. The treatment is most valuable in cases which show synovial changes rather than in those which showed marked bony change.

9. Twenty cases of general paralysis of the insane were

treated by malarial therapy.

10. 45% of the cases were observed to have benefited by this treatment for a period of at least twelve months after injection.

11. One case died as a direct result of malarial treatment. Patients must be carefully selected for this treatment.

12. Improvement in the blood and cerebro-spinal fluid is sometimes observed after treatment.

13. Best results were obtained when anti-syphilitic treatment was given before and after malaria.

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